REMARKS

Claims

Claims 1, 2, 4–7 and 9–11 are currently under examination with claims 8 and 12–24 withdrawn from consideration due to restriction/election. Claim 3 is cancelled without prejudice or disclaimer.

Claim Amendments

Support for the amendment of the claims can be found in, for example, page 18, lines 8–17 of the originally filed specification and the disclosure contained in the Examples. See also, original claim 17.

Restriction/Rejoinder

Instant claims 14–18 are directed to the pharmaceutical composition(s) of the instant invention and read on the elected species. Claim 24 explicitly recites the elected species. See, page 5 of the Restriction Requirement mailed April 20, 2006 and Applicants' Reply filed July 18, 2006. It is not understood why the claims are directed to *non-elected subject matter*, as alleged in the Office Action. Favorable action is earnestly solicited.

Withdrawn claims 22–23 are drawn to a method of using the compositions of claim 1 and recite all the elements of Applicants' composition claims. As noted previously, these are eligible for rejoinder upon allowance of generic product claims. See M.P.E.P. § 806.05.

Rejection under 35 U.S.C. §103(a)

The rejection of claims 1-7, and 9-11 under 35 U.S.C. §103(a) as allegedly unpatentable over Thorpe (US 6,703,020) is respectfully traversed.

In maintaining this rejection, the Office Action continues to contend that Thorpe teaches the claimed combination. In page 4, ¶1 of the Office Action, it is stated that saturation of the Tie2 receptors by angiopoietin-1 ligand would inhibit binding of the angiopoietin-2 ligand to the receptor, thereby the "combined effect would be inhibition of VEGF [production]." Based on Thorpe's teaching that "perpetual angiopoietin-2 signaling may well obliterate the effects of both angiopoietin and VEGF (emphasis added)," the Examiner alleges that the disclosure in USP'020 *prima facie* renders obvious the claims of the present application. Applicants disagree with this allegation. The cited reference is absolutely silent regarding the use of non-identical compounds (i.e., compounds I and II) for VEGF and Angiopoietin-2 receptor modulation, as is explicitly recited in the instant claims. The skilled worker is not motivated to use two different compounds because Thorpe's

teaching only guides or suggests a single modulator of angiopoietin-2 receptor system. As such, Thorpe cannot render obvious the claims of the present application.

Even if the Examiner's contention's regarding the *possibility* of a simultaneous modulation of both the Tie receptor system as well as VEGF receptor system (via saturation with angiopoietin-1 ligand) were taken at face value, Thorpe still fails to render obvious the claims of the present application. The scientific evidence presented in Examples 1–4 of the instant application point to a superior tumoricidal effect(s) of the claimed combination of VEGF and Tie-2 receptor modulators over sole VEGF or Tie-2 receptor modulators. To this end, Applicants' specification expressly teaches that the modulation of the two receptor systems unexpectedly results in superior pharmacological effects. See, for example, page 5, lines 23–26 of the instant specification and the experimental data contained in Examples 1–2 (Figs. 1 and 2). In these studies, the effects of the elected combination (i.e., wherein compound I is 4-Chlorophenyl)[4-(4-pyridylmethyl)-phthalazin-1-yl]ammonium hydrogen succinate and compound II is sTie2) over sole agents (i.e., compound I or compound II) were analyzed using two different end-point metric techniques. In Example 1, the average time needed for ectopic melanoma tumors to reach an end-point size in mice bearing such tumors was studied. In Example 2, average tumor volumes tumor volume in the tumor bearing mic after a given time period was analyzed.

As summarized in Fig. 1, the average time needed for ectopic melanoma tumors to reach an end-point size of 250 mm^2 in mice was 24 days for control group (no treatment) and 31 days for mice receiving monotherapy (i.e., angiopoietin inhibitor or VEGF kinase inhibitor). A combination of both angiopoietin inhibitor and VEGF kinase inhibitor increased this time period to 38 days. Corollary studies involving measurement of tumor volume after a given time period (28 days) in control and treated (both monotherapy and combined therapy) mice show similar results. See, the experimental data contained in Fig. 2. In these studies, average tumor volume of ectopic melanoma cells in control group after 28 days was 1000 mm^3, while in mice treated with anti-VEGF antibody (compound I, which is different from the one used in Example 1) or sTie2 (compound II) was 450 mm^3 and 600 mm^3, respectively. In mice receiving a combination of compounds I and II, the tumor volume was 250 mm^3. See, the paragraph bridging pages 24 and 25 of the originally-filed specification.

Applicants further note that the effect of other representative species of VEGF/R system modulators and/or Tie-2 system modulators was consistent with the two aforementioned compounds. To this end, Example 3 of the present application examines the effect of a single chain antibody recognizing the VEGF-VEGFR complex conjugated to a truncated tissue factor (scFv-tTf) (compound I, which is different from the one used in Examples 1 and 2) in combination with sTie2

(compound II). As summarized in page 27, ¶1 of the originally filed specification, average tumor volume of ectopic melanoma cells in control group after 28 days was 1000 mm^3, while in mice treated with sc-Fv-tTf (compound I) or sTie2 (compound II) was 500 mm^3 and 600 mm^3, respectively. In mice receiving a combination of compounds I and II, the tumor volume was 300 mm^3. The results indicate that a combination of the present invention inhibits tumor growth *in vivo* and the inhibitory effect thereof is greater than the effect of *singular* compounds.

Additionally, in Example 4 of the present application, the *in vivo* tumoricidal effect of 4-Chlorophenyl)[4-(4-pyridylmethyl)-phthalazin-1-yl]ammonium hydrogen succinate, either solely or in combination with sTie2 was studied. Results are consistent with other species of VEGF and Tie-2 receptor modulators, as discussed in the aforementioned paragraphs. See, page 29 of the originally-filed specification.

These studies directly refute the Examiner's basis for *prima facie* case of obviousness. The effect of the claimed combination is superior over sole use of VEGF modulators and/or Tie-2 modulators. The claimed combinations and/or pharmacological effect thereof involve *more than* the sole use of the claimed modulators. These data in the Examples unequivocally demonstrate that combined modulation of VEGF/VEGF receptor systems and Angiopoietin/Tie receptor system, leads to an unexpected tumoricidal effect. Such an effect is in no manner suggested by the reference of record.

In view of the above remarks, it is respectfully submitted that Thorpe, even at its broadest interpretation, fails to render obvious the subject matter of the present invention. Withdrawal of the rejection is respectfully submitted.

Regarding instant claims 10 and 11, it is respectfully submitted that insofar as the cited reference is silent with respect to the combination recited in Applicants' independent claim 1, the subject matter in these claims is also unobvious over the disclosure contained in the art references of record.

In view of the above remarks, favorable reconsideration is courteously requested. If there are any remaining issues which could be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below.

The Commissioner is hereby authorized to charge any fees associated with this response to Deposit Account No. 13-3402.

Respectfully submitted,

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